Implications of PRESERVING LONG-TERM RENAL FUNCTION After Renal Transplantation

Presented by:

National Institute of Allergy and Infectious Diseases of
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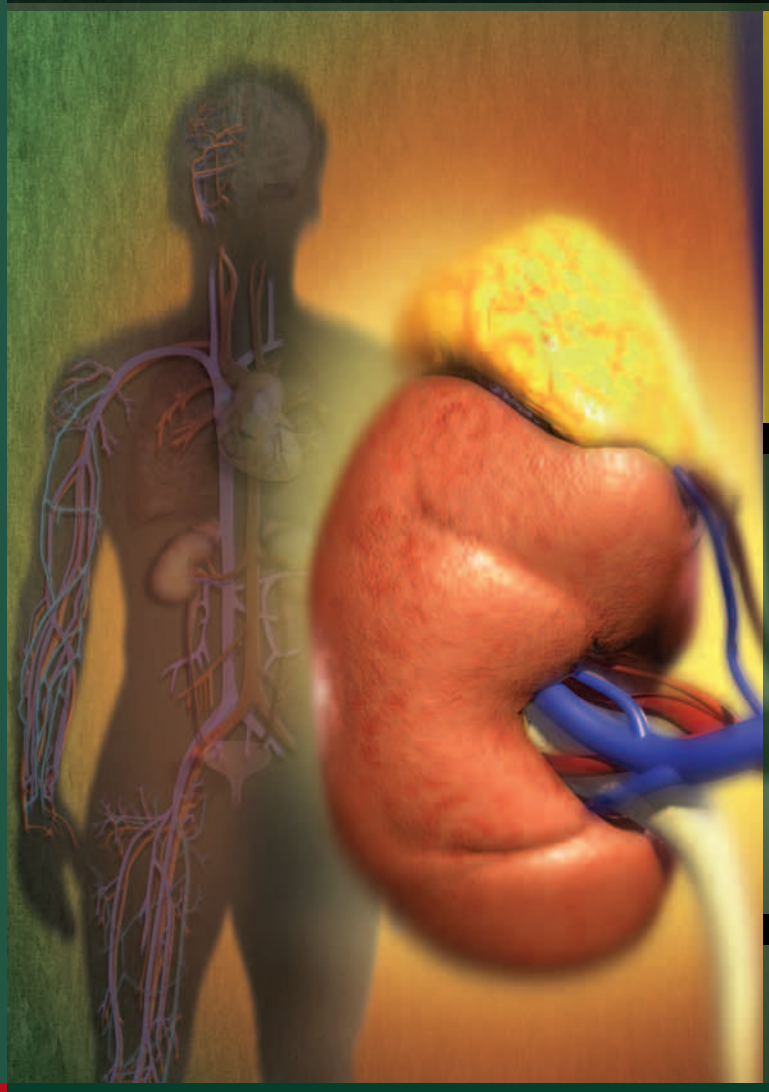
Understanding the Relationship Between Renal Dysfunction and Cardiovascular Disease After Renal Transplantation



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Target Audience

Transplant surgeons, transplant nephrologists, transplant nurses, transplant coordinators, and other healthcare professionals who are involved in the treatment and management of renal transplant recipients.

Educational Objectives

This monograph will provide current information regarding the:

- Associations between renal dysfunction and traditional and nontraditional cardiovascular disease risk factors
- Prevalence of cardiovascular disease and cardiovascular mortality in patients with chronic kidney disease and in renal transplant recipients
- Strong relationship between renal function and graft and patient survival in renal transplant recipients
- Role of accurate assessment of graft function and diagnosis of rejection and other conditions following renal transplantation in optimizing graft and patient survival
- Possible links between immunosuppressive protocols and kidney failure and cardiovascular disease risk in renal transplant recipients
- Implications of current knowledge for the refinement of renal transplant recipient management strategies to reduce the burden of cardiovascular disease and to improve long-term graft and patient survival.

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Presented By

National Institutes of Health
National Institute of Allergy and Infectious Diseases
Division of Allergy, Immunology, and Transplantation
Bethesda, Maryland

Represented By

Shiv A. Prasad, PhD
Chief, Transplantation Immunobiology Branch
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland

Program Co-Chairs

Donald E. Hricik, MD
Chief, Division of Nephrology
Case Western Reserve University
University Hospitals of Cleveland
Cleveland, Ohio

Marc I. Lorber, MD
Professor of Surgery and Pathology
Section Chief, Organ Transplantation and Immunology
Yale University School of Medicine
New Haven, Connecticut

Faculty

Stuart M. Flechner, MD
Professor of Surgery
Director of Clinical Research
Section of Renal Transplantation
Cleveland Clinic Lerner College of Medicine
Case Western Reserve University
Cleveland, Ohio

Bruce Kaplan, MD
Professor of Medicine and Pharmacology
Medical Director Renal and Pancreas Transplantation
University of Florida
Gainesville, Florida

Bertram L. Kasiske, MD
Professor of Medicine
University of Minnesota
Minneapolis, Minnesota

Akinlolu O. Ojo, MD, PhD
Associate Professor of Medicine
Division of Nephrology
University of Michigan
Ann Arbor, Michigan

Kim Solez, MD
Professor of Pathology
University of Alberta
Alberta, Canada

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Introduction

Chronic kidney disease is a major public health problem in the United States.[1,2] This disease is prevalent among adults and is associated with high rates of hospitalization, morbidity, and mortality.[3] The major outcomes of chronic kidney disease are (1) progressive loss of renal function leading to various complications and kidney failure, and (2) development of cardiovascular disease.[1] Early detection of a progressive kidney disease may allow prevention or delay of complications. Established risk factors for chronic kidney disease include diabetes, hypertension, and family history of kidney disease.[1,2] It has been shown that African Americans, Hispanics, Native Americans and individuals aged 60 years and older are at increased risk for chronic kidney disease.[1]

The link between renal function and cardiovascular disease is both troubling and intriguing. Even mild declines in renal function appear to elevate the risk of cardiovascular disease.[4,5] Chronic kidney disease is associated with coronary artery disease (CAD), left ventricular hypertrophy (LVH), and congestive heart failure (CHF).[6] The prevalence of cardiovascular disease is higher in both end-stage renal disease (ESRD) patients and renal transplant recipients than in the general population.[7] Furthermore, cardiovascular disease is the most frequent cause of death in ESRD patients and renal transplant recipients.[6,7]

In renal transplant recipients, rates of short-term graft and patient survival following transplantation continue to improve. Long-term outcomes, however, have improved at a much slower pace.[3] Immunosuppressive regimens, which have clearly contributed to improved graft and patient survival over time,[8] may elevate cardiovascular disease risk through detrimental effects on kidney function, blood pressure, and serum lipid and blood glucose levels.[2,9]

Research is providing important clues to the causes of cardiovascular morbidity and mortality in patients with chronic kidney disease and in renal transplant recipients. This monograph will present the findings of many of these studies. Both traditional and nontraditional cardiovascular disease risk factors appear to contribute to cardiovascular disease morbidity and mortality.[10,11] In addition, renal function within the first year after renal transplantation is an important predictor of long-term graft survival and a strong risk factor for cardiovascular death.[12,13]

To further understand the link between kidney failure and cardiovascular disease, the National Institute of Diabetes and Digestive and Kidney Diseases has initiated the Chronic Renal Insufficiency Cohort (CRIC) study, a multicenter, national, longitudinal study of renal insufficiency and cardiovascular disease designed to examine patterns of comorbidity and shared risk factors. The objective is to reduce the burden of advanced kidney disease and cardiovascular disease by identifying and treating those individuals at highest risk of comorbidity.[14]

The knowledge gained from this study and the studies described in this monograph, augmented by ongoing investigations, will allow development of management strategies to reduce the cardiovascular disease burden and improve long-term outcomes in patients with chronic kidney disease and in those undergoing renal transplantation.

Incidence of Chronic Progressive Kidney Disease and Association with Cardiovascular Disease

The incidence of chronic progressive kidney disease in the United States is increasing. Preventing cardiovascular disease in patients with early kidney disease, who are often asymptomatic, presents an enormous challenge.[14] Of the approximately 8 million Americans who have chronic kidney disease, only 300,000 are in kidney failure.[2] The remainder are at high risk for cardiovascular disease, yet are far more difficult to identify and monitor.

The Glomerular Filtration Rate (GFR) is widely accepted as the best overall measure of renal function.[2] In patients with chronic kidney disease, renal function decreases over time. The GFR is calculated from equations that take into account the serum creatinine concentration and variables such as age, gender, race, and body size. Data from the Third National Health and Nutrition Examination Survey (NHANES III), a prospective study of a large representative sample of the general population in the United States, indicate that approximately 8 million adults (persons aged 20 years and older) have chronic kidney disease (Table 1).[1,2,15] as defined by the National Kidney Foundation (NKF) criteria:

Table 1

Stages and Prevalence of Chronic Kidney Disease (Age ≥20 yr)(National Kidney Foundation/K/DOQI/S20)

Stage	Description	GFR (mL/min/1.73m²)	Prevalence* N (1000s)	Prevalence* %
1	Kidney damage with normal or ↑ GFR	≥90	5,900	3.3
2	Kidney damage with mild ↓ GFR	60-89	5,300	3.0
3	Moderate ↓ GFR	30-59	7,600	4.3
4	Severe ↓ GFR	15-29	400	0.2
5	Kidney failure	<15 (or dialysis)	300	0.1

*Data for Stages 1-4 from NHANES III (1988-1994)[1]. Population of 177 million adults age ≥20 years. Data for Stage 5 from USRDS (1998)[2] include approximately 230,000 patients treated by dialysis, and assume 70,000 additional patients not on dialysis. GFR estimated from serum creatinine using MDRD Study equation based on age, gender, race and calibration for serum creatinine. For Stages 1 and 2, kidney damage estimated by spot albumin-to-creatine ratio >17 mg/g in men or >25 mg/g in women on two measurements.

[1]Coresh et al. *Am J Kidney Dis*. 2003;41:1-13.

[2]Data for Stage 5 from USRDS (1998).

- GFR <60 mL/min/1.73 m^2, which indicates a loss of one-half or more of normal adult kidney function, for ≥3 months, with or without kidney damage, or
- Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without a decreased GFR, demonstrated by pathological abnormalities or markers of kidney damage.[1,2]

The NKF Kidney Disease Outcomes Quality Initiative (K/DOQI), which provides evidence-based clinical practice guidelines for kidney disease diagnosis and management, has established a classification system for chronic kidney disease.[2,16] The K/DOQI guidelines classify Stage 1 disease as kidney damage with normal or increased GFR (≥90 mL/min/1.73 m^2), mild decreases in GFR (60-89 mL/min/1.73 m^2) as Stage 2 disease, and moderate decreases in GFR (30-59 mL/min/1.73 m^2) as Stage 3 disease. Stage 4 disease is marked by severely decreased GFR (15-29 mL/min/1.73 m^2), while stage 5 disease is kidney failure (GFR <15 mL/min/1.73 m^2 or dialysis). The prevalence of stages 1 through 4 is more than 100 times greater than the prevalence of stage 5 or kidney failure.[1,2]

Patients with chronic kidney disease are at high risk for cardiovascular disease. In a US Renal Data System (USRDS) study, patients without cardiovascular disease were followed for one year to determine the rate at which they developed cardiovascular disease.[3] In the 1-year study period patients with chronic kidney disease (n=6463) were 1.6 times more likely to develop cardiovascular disease than those without chronic kidney disease (n=533,059).

Chronic kidney disease has been associated with CAD and LVH, which are precursors of cardiovascular disease morbidity and mortality.[6] Patients with chronic kidney disease also have a high prevalence of CHF, an independent predictor of death in chronic kidney disease.[6]

The Link Between Kidney Disease, Cardiovascular Disease, and Death

Although overlap between risk factors for chronic kidney disease and risk factors for cardiovascular disease is evident, overlap alone cannot account for the greatly increased risk of cardiovascular morbidity and mortality observed in patients with chronic kidney disease.[11] Cardiovascular disease is actually more common in this population than is kidney failure.[1] Ongoing studies will improve our understanding of the interrelationships between chronic kidney disease, cardiovascular disease, and mortality. Clinical trials are also attempting to identify modifiable cardiovascular disease risk factors in patients with chronic kidney disease.

The Heart Outcomes and Prevention Evaluation (HOPE) study, a double-blind, randomized, multinational trial, included 9297 men and women aged 55 and older with vascular disease or diabetes combined with one other cardiovascular risk factor.[17] Patients with serum creatinine >2.3 mg/dL or proteinuria were excluded from the study. As shown in Table 2, the rates of cardiovascular mortality, overall mortality, and hospitalization for CHF among patients with kidney failure (serum creatinine ≥1.4 mg/dL) were nearly twice those of patients without kidney failure. Cardiovascular disease risk was positively correlated with higher serum creatinine levels. These results suggest that mild renal insufficiency is a risk factor for future cardiovascular events in patients with other risk factors for cardiovascular disease. Of further note, the risk for cardiovascular disease in patients with mild renal insufficiency was independent of other known risk factors, such as diabetes, hypertension, and microalbuminuria.[17]

In the Hypertension Detection and Follow-up Program (HDFP), a cohort of 10,940 persons with hypertension was studied for a period of 5 years.[18] In this cohort, serum creatinine levels ≥1.7 mg/dL at baseline were associated with a 2.2-fold higher adjusted odds of death at 8 years in patients aged 30 to 69 years.[18] The risk of death increased linearly with rising serum creatinine levels; furthermore, cardiovascular disease was the most frequent cause of death in patients with elevated serum creatinine levels.

The baseline level of serum creatinine also was an important and significant risk factor for 8-year mortality.[18] The risk in the group with the highest serum creatinine level was 5 times that of the group with the lowest serum creatinine level. Mean serum creatinine levels were also higher for men than for women and higher for African Americans than for Caucasians. In summary, serum creatinine level was found in this study to be a significant, independent predictor of mortality in a hypertensive population.[18]

Table 2

The HOPE Trial: Renal Insufficiency and Cardiovascular Outcomes

Outcome	CRI (%) (n=980)	No CRI (%) (n=8307)	*P*
Acute MI	16.3	10.5	<.001
Stroke	5.0	4.0	<.07
CVD death	11.4	6.6	<.001
All death	17.8	10.6	<.001
Hospitalized CHF	6.0	2.9	<.007
Revascularization	19.6	16.9	.08

CRI indicates chronic renal insufficiency; MI, myocardial infarction; CVD, cardiovascular disease; CHF, congestive heart failure.

Adapted with permission from Mann JFE, Gerstein HC, Pogue J, Bosch J, Yusuf S, for the HOPE Investigators. *Ann Intern Med*. 2001; 134:629-636.

The Hypertension Optimal Treatment (HOT) study followed 18,790 patients with hypertension for an average period of 3.8 years.[19] In this population, baseline serum creatinine levels >1.5 mg/dL were associated with increased risk of all major cardiovascular events, cardiovascular mortality, and total mortality (Table 3).[19]

In the Framingham Heart Study, the probability for hypertension treatment in a large general population sample (n=6233) increased by 75% in men and by 42% in women when serum creatinine levels were elevated (≥1.5 mg/dL for men and ≥1.4 mg/dL for women).[20] Mortality rates were higher compared to those with normal kidney function in both men (*P*=.003) and women with kidney failure, although the association was not statistically significant in women after age adjustment.[21]

Associations Between Mild-to-Moderate Renal Dysfunction, Cardiovascular Disease, and Cardiovascular Risk

Several studies have found that milder degrees of renal dysfunction are associated with cardiovascular morbidity and mortality. The identification of these relationships opens the door for applying measures of renal function (eg, serum creatinine) to predict cardiovascular disease. This practice may be particularly useful for developing preventive assessment and intervention strategies for persons with early kidney disease, in whom clinical manifestations may not yet be evident.

The association between renal function and survival after myocardial infarction (MI) was investigated in 130,099 elderly patients (aged 65 years and older) enrolled in the Cooperative Cardiovascular Project.[22] As shown in Figure 1, patients with normal renal function had a 1-year survival rate of 76%, compared with 54% in patients with mild renal insufficiency and 34% in patients with moderate renal insufficiency (*P*<.001). A substantially elevated risk of death was observed in the first month of follow-up after MI for individuals with mild and moderate renal dysfunction; this risk remained elevated during the first 6 months post-MI and was independent of other cardiovascular disease risk factors.[22]

An increase in 1-year mortality was associated with decreasing renal function in 5327 patients undergoing percutaneous coronary intervention at the Mayo Clinic.[23] The association was important even in patients with mild renal insufficiency (creatinine clearance ≥70 mL/min), with a doubling of mortality at 1 year.[23] The increased mortality risk rose proportionately with the severity of renal insufficiency and was independent of other cardiovascular risk factors. The relative risk of death during follow-up was highest for patients on dialysis, followed by patients with moderate renal dysfunction.[23]

In the Cardiovascular Health Study, a longitudinal population-based study of 5808 subjects aged >65 years, elevated serum creatinine levels were predictive

Table 3

Cardiovascular Events and Mortality According to Baseline Serum Creatinine in the Hypertension Optimal Treatment (HOT) Study

Events	No. of Events	Event/ 1000 Patient Years	Adjusted Relative Risk	95% CI	*P*
Major cardiovascular events					
Creatinine ≤ 1.5 mg/dL	626	9.2			
Creatinine > 1.5 mg/dL	45	27.0	2.05	1.47-2.88	<.001
All Myocardial infarction					
Creatinine ≤ 1.5 mg/dL	197	2.9			
Creatinine > 1.5 mg/dL	8	4.7	1.44	0.70-2.93	.32
All Stroke					
Creatinine ≤ 1.5 mg/dL	273	4.0			
Creatinine > 1.5 mg/dL	16	9.5	1.58	0.88-2.84	.13
Cardiovascular mortality					
Creatinine ≤ 1.5 mg/dL	241	3.5			
Creatinine > 1.5 mg/dL	28	16.4	3.24	2.13-4.94	<.001
Total mortality					
Creatinine ≤ 1.5 mg/dL	532	7.8			
Creatinine >1.5 mg/dL	50	29.3	2.86	2.10-3.89	<.001

P values, between risk ratios, and confidence intervals. CI, confidence intervals.
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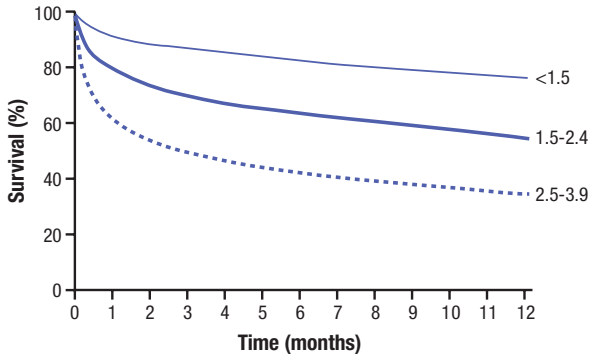
Figure 1

Unadjusted 1-Year Survival for 130,099 Patients After Myocardial Infarction by Initial Serum Creatinine Levels (mg/dL)



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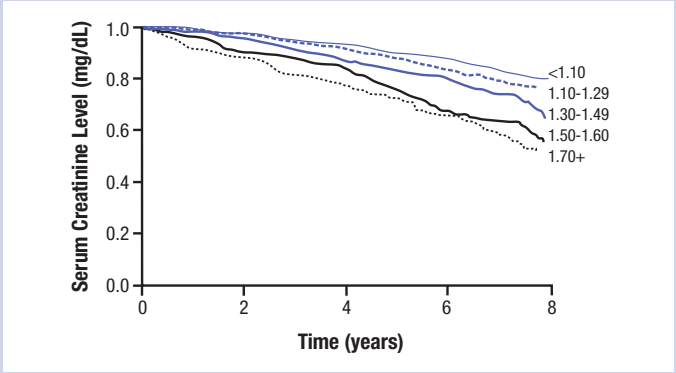
of cardiovascular disease events and mortality.[5] An elevated baseline serum creatinine level (≥1.5 mg/dL for men and ≥1.3 mg/dL for women) was observed in 11.2% of the study population. Elevated creatinine was associated with a high prevalence of cardiovascular disease risk factors and a significantly increased risk for all-cause mortality, cardiovascular mortality, and cardiovascular morbidity, even after adjustment for cardiovascular disease risk factors and existing diseases (Figure 2).[5] The increased risks for mortality, cardiovascular disease, and CHF increased linearly with rising creatinine levels and were apparent with early kidney disease.

The relationship between mild to moderate renal insufficiency and the risk for coronary heart disease events was evaluated in the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal women with established coronary artery disease.[4] The participants in the HERS trial were postmenopausal women with established coronary artery disease. Higher serum levels of triglycerides and lipoprotein(a) were measured in 2579 women with mild (serum creatinine level 1.2-1.4 mg/dL) and moderate (serum creatinine level >1.4 mg/dL) renal insufficiency compared to 182 women with normal renal function (serum creatinine ≤1.2 mg/dL) [Table 4].[4] After adjusting for multiple variables, both mild and moderate renal insufficiency were shown to be independently associated with an increased risk for cardiovascular events (including death from coronary heart disease, nonfatal MI, and hospitalization for unstable angina, stroke, and transient ischemic attacks).

Many traditional cardiovascular risk factors, including advanced age, hypertension, hyperlipidemia, diabetes, and physical inactivity, are more prevalent in patients with chronic kidney disease and likely contribute to cardiovascular disease.[6] Hemodynamic and metabolic changes that accompany chronic kidney disease, such as proteinuria, increased extracellular fluid volume, and electrolyte imbalance, also may increase cardiovascular disease risk. Recent studies suggest that nontraditional risk factors may play a role as well (Table 5).[10,11] While these factors appear to be associated with chronic kidney disease, additional studies are needed to determine if they are a cause or a result of kidney failure, and if and how they influence the progression of kidney disease or development of cardiovascular disease in patients with chronic kidney disease.

Figure 2

Age-Adjusted Survival of Subjects in the Cardiovascular Health Study By Serum Creatinine Level (mg/dL)



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Nontraditional Risk Factors

Several studies have demonstrated an association between inflammation and reduced kidney function[22,23] or atherosclerosis.[22] In nondiabetic subjects, C reactive protein (CRP), a marker for systemic inflammation, correlated with traditional cardiovascular and renal risk factors, including age, gender, blood pressure, serum cholesterol, plasma glucose, diminished filtration, and creatinine clearance.[22] In another study, CRP levels in 102 patients who were predialysis were elevated.[24-26]

Insulin resistance and hyperinsulinemia present early in the course of kidney disease.[27,28] A link between insulin resistance, cardiovascular disease risk, and cardiovascular disease mortality has been shown in patients with the metabolic syndrome. Serum uric acid levels are associated with both kidney disease and cardiovascular disease, although a causal role has not been established.[29,30] Hyperparathyroidism is linked to cardiovascular disease and renal dysfunction.[31] Patients with moderate kidney failure have elevated parathyroid hormone levels and reduced levels of vitamin D.[32,33]

Obesity is a major cause of hypertension and increases the risk for kidney disease.[34] Elevations of the peptide leptin are observed in obese individuals and have been

Table 4

Hypertension and Estrogen/Progestin Replacement Study: Characteristics of Participants By Serum Creatinine Level at Baseline

Decreased GFR and Plasma Lipids				
	Serum Cr (mg/dL)			
Baseline and Outcome	**1.2 (n=2012)**	**1.2-1.4 (n=567)**	**1.4 (n=182)**	***P***
Hypertension (%)	55	66	77	<.001
LDL (mg/dL)	145±38	145±36	147±43	.72
HDL (mg/dL)	51±13	49±13	49±14	.12
Trig (mg/dL)	160±61	168±64	182±67	.002
Lp(a) (mg/dL)	33±32	35±33	38±36	.05

Cr, creatinine; Trig, triglyceride.

Adapted with permission from Shlipak MG, Simon JA, Grady D, Lin F, Wenger NK, Furberg CD for the Heart and Estrogen/progestin Replacement Study (HERS) Investigators. *J Am Coll Cardiol*. 2001;38:705-711.

Table 5

Risk Factors for Cardiac Disease in CKD

Traditional	Nontraditional
Hypertension	↑ C-reactive protein
Diabetes	↑ Advanced glycation end products
Age	Hyperhomocysteinemia
Smoking	Hyperparathyroidism
↑ LDL cholesterol	↑ Serum uric acid
↓ HDL cholesterol	↑ Plasma leptin

linked to sympathetic nervous system activation.[34,35] Hyperleptinemia has also been associated with elevated cardiovascular disease risk.[33] Other research suggests that leptin may contribute to cardiovascular disease risk through an effect on lipid metabolism.[34] Research suggests that the hypertension induced by excess weight gain may be caused by activation of the sympathetic nervous system.[36]

Data from NHANES III documented links between several nontraditional cardiovascular disease risk factors and chronic kidney disease.[10] In this large, general population sample, lower GFR was associated with decreased levels of apolipoprotein A1, and increased levels of apolipoprotein B, plasma fibrinogen, homocysteine, and CRP.

Implications for Management of Renal Transplant Recipients

Impact of the Modality of Renal Replacement Therapy on Cardiovascular Disease

Correlations between kidney failure and cardiovascular risk factors have important implications for the management of renal transplant recipients. Renal transplant recipients typically have GFRs below normal as a result of previous rejections, the occurrence of chronic allograft nephropathy, donor-related factors, or issues related to the graft.[37,38] These patients may also have a high incidence of cardiovascular disease.[7]

The life expectancy for patients with ESRD is substantially lower than that of the general population, regardless of treatment approach.[3] According to the USRDS, expected remaining lifetimes for patients on dialysis are one-third to one-sixth of those in the general population. Renal transplantation provides a clear survival benefit as expected lifetimes for transplant recipients are 2 to 3 times higher than those of patients still on dialysis.[3]

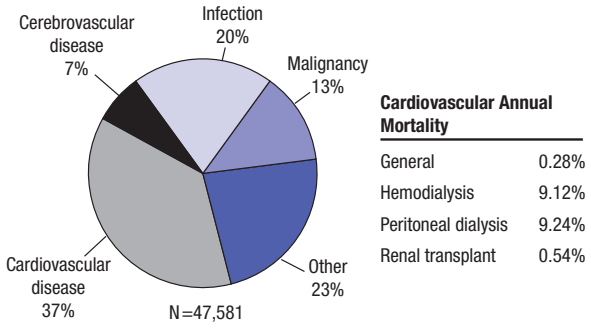
Wolfe et al and colleagues have reported an increase in survival for renal transplant recipients compared with ESRD patients on transplant waiting lists. This study analyzed USRDS data on 228,552 patients aged 0 to 69 years, who were on dialysis with newly diagnosed ESRD. Of these, 46,164 were on the transplant waiting list for the first time. Among the patients on the waiting list, 23,275 received a first cadaveric renal transplant by the end of the 5-year study period. An analysis of survival data revealed that the estimated long-term mortality risk for transplant recipients was 68% lower than that of patients on the transplant waiting list ($P<.001$), based on 3 to 4 years of follow-up.[39] In addition, projected years of remaining life for patients who remained on waiting lists and for renal transplant recipients were 10 years and 20 years, respectively.

Despite the more favorable survival of transplant recipients versus patients who are on dialysis, their expected remaining lifetimes are still considerably shorter than those of the general US population. In renal transplant recipients, cardiovascular mortality is the most frequent cause of death, followed by infection and malignancy (Figure 3).[7,9] In patients with ESRD or a kidney transplant, 40% of deaths are due to cardiovascular disease.[16] The annual cardiovascular disease mortality rate is 0.54% in renal transplant recipients, compared to 0.28% in the general population and approximately 9.0% in patients on dialysis.[7]

An analysis of survival data for 86,502 adult recipients of renal transplants between 1988 and 1997 revealed that 38.0% (n=7040) died with a functioning graft.[40] Death with functioning graft was defined as death not preceded by return to dialysis or transplant nephrectomy, no graft failure date or cause of graft failure reported, or serum creatinine at the last follow-up <4.0 mg/dL. Deaths with a functioning graft accounted for 42.5% of all graft loss and the predominant cause of death in this group was cardiovascular disease (36.1%; n=2538).[40] Almost one half of the deaths with a functioning graft occurring within 30 days after transplantation were due to cardiovascular disease, primarily MI. The risk of death with a functioning graft was considerably

Figure 3

Mortality in Renal Transplant Recipients



USRDS database, 2001.

Foley et al. *J Am Soc Nephrol*. 1998;9:S16-S23.
Foley et al. *Am J Kidney Dis*. 1998;32:S112-S119.

lower for patients undergoing renal transplantation after 1990.[40] Posttransplant patient survival was 97%, 91%, and 86% at 1, 5, and 10 years, respectively. Survival improved each year after 1988. Although the rate of graft survival has increased in recent years, early attention to and vigilant management of cardiovascular disease risk factors may further improve longevity in renal transplant recipients.

Link Between Renal Function and Cardiovascular Mortality in Renal Transplant Recipients

Cardiovascular mortality in the transplant population has been linked to reduced renal function. Such a link would help to explain the clear survival advantage of renal transplantation over dialysis in terms of cardiovascular-related mortality. Renal function following renal transplantation has been shown to predict long-term graft survival.[12] In an analysis of survival data for 105,742 patients receiving renal transplants between 1988 and 1998, renal function in the first year following transplantation emerged as the strongest predictor of long-term graft survival.[12] The patients with elevated serum creatinine at 1 year (≥1.5 mg/dL) were more likely to be African American, male, and recipients of a previous transplant.[12] These findings suggest that serum creatinine at 1 year might be a useful endpoint for primary comparative trials evaluating posttransplant management alternatives.

Meier-Kriesche et al reviewed the USRDS data for 58,900 adult renal transplant recipients who had undergone their first transplants between 1988 and 1998 to assess the impact of renal function on posttransplant cardiovascular mortality.[13] These patients had functioning grafts at 1 year posttransplantation and serum creatinine levels ≤4 mg/dL.

The most frequent cause of death was cardiovascular disease (Table 6).[13] After using Cox proportional-hazard models to correct for variables, associations between certain pretransplant cardiovascular risk factors—hypertension and diabetes—and an increased risk of cardiovascular death were noted (Table 7).[13] The time a patient spent on dialysis correlated positively to cardiovascular death, an association that was independent of hypertension or diabetes. Relative risk of cardiovascular death was also associated with the year in which the transplantation was performed. In recent years, cardiovascular death following renal transplantation has been declining, although at a similar rate to that observed in patients on dialysis and in the general population.

In this study, serum creatinine levels at 1 year posttransplantation correlated positively to risk of cardiovascular death (Figure 4).[13] More specifically, when serum creatinine levels were separated by 0.1-mg/dL increments and correlated with relative risk, a serum creatinine of 1.7 to 1.8 mg/dL was associated with a 40% independent risk for cardiovascular death. Cardiovascular events were not included. These data suggest that as renal function declines, the risk for cardiovascular morbidity and mortality slowly rises. Not surprisingly, when cardiovascular death after graft loss was included in the analysis, the association between reduced renal function and increased cardiovascular death was stronger.[13]

Table 6

Cause of Death in Primary Renal Transplant Recipients Beyond 1 Year of Transplantation

Cause of Death	N	%
All	5,963	
Cardiovascular	1,797	30.1
Infectious	698	11.7
Malignancy	603	10.1
Other	2,865	48.1

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Another factor for the clinician to consider is that some of the pharmacologic agents utilized to treat renal transplant recipients may also adversely affect renal function. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-2 receptor blockers can cause acute declines in GFR.[2] The calcineurin inhibitors cyclosporine and tacrolimus have long been associated with nephrotoxicity.[41] Renal function, therefore, is frequently monitored during administration of maintenance immunosuppressive regimens that include calcineurin inhibitors, and appropriate dose modification or even drug withdrawal may be considered in patients with significantly elevated serum creatinine levels. One study of calcineurin inhibitor and steroid dose reduction indicated that these alternatives may offer benefits to both preserve long-term renal function and reduce mortality.[42] A study of 121 renal transplant recipients; 62 receiving the sirolimus (Srl) based regimen; 59 receiving mycophenolate mofetil (MMF), and all patients receiving cyclosporin (CsA) and prednisone; treated with sirolimus in conjunction with reduced doses of calcineurin inhibitors and steroids, for example, was effective and provided excellent renal function and minimal morbidity. Among the patients who received Srl, hematopoeitic abnormalities and hyperlipidemia were observed, but readily controlled, and renal function was not adversely affected.

Renal function 1 year following renal transplantation directly correlates with long-term graft survival and cardiovascular mortality. A cardiovascular benefit is recognized with the improvement of renal function that is achieved through transplantation. These findings suggest the need to refine the approach to transplant recipient care and to emphasize measurement and optimization of graft function along with prevention of rejection.

Role of Allograft Biopsy in Diagnosis of Rejection and Disease in the Transplanted Kidney

A variety of factors and conditions can increase cardiovascular disease risk in the posttransplant period. As discussed previously, a poorly functioning graft may be associated with anemia, hypertension, hyperlipidemia, hyperhomocysteinemia, diabetes mellitus, or glucose intolerance, all of which may contribute to cardiovascular disease risk.[43]

Clinical examinations and laboratory tests are important tools for monitoring patients following renal transplantation. Pathology, however, remains the gold standard for diagnosis of rejection and assessment of other disease conditions in the transplanted kidney. The Banff Classification is a schema that was developed to standardize interpretation of renal allograft biopsies.[44] This classification schema, first published in 1993, is refined every 2 years at consensus conferences. It has been validated in clinical studies and is widely used internationally today.

Standardization of renal allograft biopsy interpretation is necessary to guide therapy and can establish an objective endpoint for clinical trials.[44] According to the Banff `97 Classification schema, kidney rejection is based on 2 main lesions: arteritis and tubulitis. These lesions are scored on a scale of 0 to 3+. Other lesions are scored to determine borderline changes, calcineurin-inhibitor–related toxicity, chronic allograft nephropathy, and other pathologic changes. Renal allograft biopsy can also help to diagnose subclinical rejection; this condition, which may occur in up to 35% of normally functioning grafts, is accompanied by moderate to severe tubulitis.[45] Without appropriate treatment, subclinical rejection can increase renal dysfunction and may lead to graft loss. The potential for detection of subclinical rejection through renal allograft biopsy raises important questions: When should biopsies be performed, and how should subclinical rejection be treated? The Banff Classification schema also establishes criteria for specimen adequacy, sampling, and staining.

Although rejection-related changes are the focus of the Banff `97 schema, it also helps to diagnose non-rejection–related conditions that may be amenable to therapy. Furthermore, the Banff schema can help to differentiate acute rejection from disease processes that cause inflammatory changes in the transplanted organ.[44] Finally, toxic effects of calcineurin inhibitors may also be detected via renal allograft biopsy.

Table 7

Cox Model for Cardiovascular Death After Transplantation

Variable	RR	CI	*P*
Recipient Age (yr)	1.053	1.049-1.058	<.001
African American Recipient	0.88	0.77-0.99	.048
Cause of ESRD (GN)	(1)		
Hypertension	1.61	1.36-1.92	<.001
Diabetes	3.78	3.26-4.38	<.001
ESRD Time (preemptive)	(1)		
<6 months	1.28	1.04-1.57	.018
6-12 months	1.30	1.07-1.57	.009
12-24 months	1.37	1.14-1.64	.001
>24 months	1.51	1.26-1.81	<.001
Living Donation	0.86	0.74-0.98	.028
Transplant year (yr)	0.95	0.92-0.98	<.001
Cr at one year (≥1.2)	(1)		
1.3-1.4	1.03	0.89-1.20	.686
1.5-1.6	1.19	1.02-1.39	.025
1.7-1.8	1.37	1.16-1.62	<.001
1.9-2.1	1.49	1.25-1.76	<.001
2.2-2.5	1.67	1.38-3.03	<.001
2.6-4.0	2.26	1.85-2.75	<.001

Cr, creatinine

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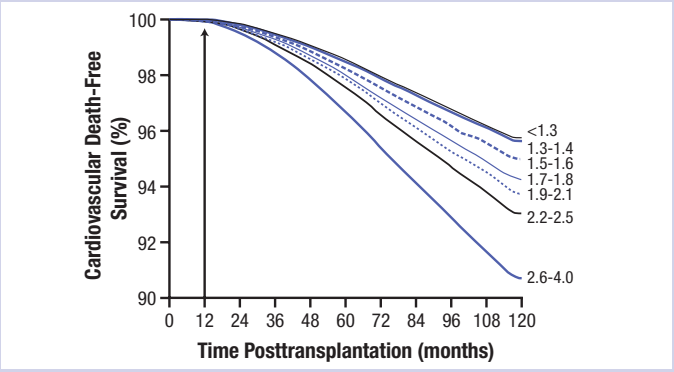
Factors Contributing to Cardiovascular Disease in the Renal Transplant Recipient

A number of studies suggest that traditional and nontraditional risk factors, in both the pretransplant and posttransplant periods, likely contribute to cardiovascular morbidity and mortality in renal transplant recipients. Cardiovascular risk in this population may be influenced by anemia and LVH, hypertension, posttransplant diabetes mellitus (PTDM), and dyslipidemia.[43,46-48] More recently identified, nontraditional cardiovascular disease risk factors, such as CRP, homocysteine, advanced glycation end products (AGEs), and thymocyte (T)-cell mediated immunodeficiency, may also be important.[49-51] Extracellular fluid volume overload, electrolyte imbalance, and oxidative stress may play a role as well.[11] Immunosuppressants may contribute to cardiovascular

Figure 4

Cardiovascular Death By Serum Creatinine Level at 1 Year Posttransplantation (mg/dL)



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disease risk through detrimental effects on renal function, hemoglobin levels, elevated blood pressure, serum lipids, and blood glucose levels (Table 8).[9,52,53]

Kiberd et al estimated the future risk of fatal and nonfatal cardiovascular disease events in a renal transplant population if "optimal" measures were applied to correct existing modifiable cardiovascular disease risk factors (eg, hyperlipidemia, hypertension).[53] The study population consisted of 439 kidney transplant recipients with a functioning graft for >6 months. Patient information about cardiovascular disease history, cardiovascular disease risk factors, and current medication use was collected through retrospective chart review. A statistical model, which employed cardiovascular mortality risk equations based on the Framingham study risk calculator, was applied. The results demonstrated that, despite optimal treatment with lipid-lowering and antihypertensive therapies, the overall risk of fatal and nonfatal cardiovascular disease events within 10 years in male study participants was much higher in renal transplant recipients than in the general population. However, optimal treatment was associated with a lower mortality risk of cardiovascular events compared with the mortality risk for "current" patients (those whose treatments were unchanged).[54] These data suggest that renal transplantation confers an increased risk of cardiovascular events that persists despite correction or reduction of traditional risk factors.

Table 8

Side Effect Profiles of Immunosuppressive Drugs

	CsA	Tac	Srl	Ster	MMF
Hypertension	++	+	∅	++	∅
Hyperglycemia	+	++	∅	+++	∅
Renal insufficiency	++	++	∅	∅	∅
Hyperlipidemia	++	+	+++	++	∅
Hyperkalemia	+++	+++	∅	∅	∅
Tremor	∅	+	∅	∅	∅
Hirsutism	+	∅	∅	∅	∅
Gingival hyperplasia	+	∅	∅	∅	∅
Hypophosphatemia	++	++	+	∅	∅
Osteoporosis	±	±	∅	+++	∅
Malignancy	+	+	?	∅	+

CsA, cyclosporin; Tac, tacrolimus; Srl, Sirolimus; Ster, Steroids; MMF, mycophenolate mofetil.

Adapted from Dr Martin Zand, University of Rochester.

Anemia and left ventricular hypertrophy

Anemia (hemoglobin levels ≤13 g/dL for men and ≤12 g/dL for women) occurs in up to 30% of renal transplant recipients and increases significantly in incidence with time after transplantation.[53,55] The etiology of post-transplant anemia is multifactorial but most closely related to graft dysfunction.[53] Persisting anemia may be a risk factor for cardiovascular disease morbidity and mortality following renal transplantation.[37] Anemia also can contribute to LVH,[47] which has been shown to be a significant predictor of CHF and death in the renal transplant population.[47]

Vanrenterghem and colleagues investigated the prevalence and management of anemia in renal transplant recipients by surveying data for 4263 patients at 72 transplant centers in Europe.[53] At enrollment, 38.6% of the patients were anemic (as previously defined), yet only 17.8% of those with the most severe anemia (8.5%) were receiving erythropoietin treatment. Lower hemoglobin levels were associated strongly with reduced renal function. Of 904 patients with serum creatinine levels >2.0 mg/dL, 60.1% were anemic compared with 29% of patients with serum creatinine levels ≤2 mg/dL (P<.01).

The use of ACE inhibitors and angiotensin II receptor antagonists was associated with a higher likelihood of anemia.[53] (Patients who were being treated with these agents for posttransplant erythrocytosis were excluded.) The patients received a variety of immunosuppressants, alone or in various combinations. Immunosuppressive protocols that included mycophenolate mofetil or azathioprine were associated with lower mean hemoglobin levels (13.1±1.9 g/dL) than regimens without these agents (13.4±2.0 g/dL; P<.01).[53] The lowest mean hemoglobin levels were found in patients who received mycophenolate mofetil in combination with steroids (12.6±1.6 g/dL).

A recent report by Mix et al noted an evolution of anemia in 241 kidney transplant recipients over a 60-month period at a single institution.[38] Anemia was prevalent in the early posttransplant period. More specifically, at least 70% of recipients had some degree of anemia in the first 6 months following transplantation.[38] Blood loss during surgery and multiple phlebotomies can contribute to anemia early in the posttransplant period. The proportion of patients with anemia declined at about the 6-month mark, and then rose again, reaching a frequency of approximately 30%.[38] A higher GFR at 3 and 6 months was consistently associated with a lower likelihood of anemia at 6 and 12 months (Figure 5).

Left ventricular hypertrophy may predict subsequent CHF and death in renal transplant recipients. Rigatto et al monitored LVH in 473 renal transplant recipients free of heart disease 1 year after transplantation.[47] Left ventricular hypertrophy in the first year following transplantation was found to be an independent risk factor for subsequent CHF and for death.[47] Persistent or de novo LVH was a strong independent risk factor for death after 5 years (Table 9).[47] Blood pressure and anemia

emerged as risk factors for left ventricular growth.[47] These data suggest that during the posttransplant period, hypertension and anemia promote LVH, predisposing the patient to CHF and death.

Levin et al provided further support for the relationship between anemia and LVH, in a study which revealed a high prevalence of LVH in 446 patients who were not transplant recipients. These patients (from a general population) with mild to moderate impairment of renal function were followed over a 12-month period at 8 centers.[56] The prevalence of LVH was 34% at study entry and 38% at 12 months. Left ventricular hypertrophy correlated with declining renal function and rose to 38% at 12 months. Left ventricular mass index (LVMI) increased by >20% of baseline values from baseline to 12 months in 25% of the study population. Increased systolic blood pressure and, to an even greater degree, anemia, are associated with LVH. A greater decrease in hemoglobin was observed in patients receiving ACE inhibitor therapy compared with those not receiving ACE inhibitors, despite similar baseline hemoglobin levels in the 2 groups.[56]

In a study of patients with type 1 diabetes, anemia during the 6-month period following kidney or pancreas-kidney transplantation was associated with a significantly increased risk for cardiovascular events in 404 patients.[46] Cardiovascular events included MI, death, or hospitalization for angina or CHF.

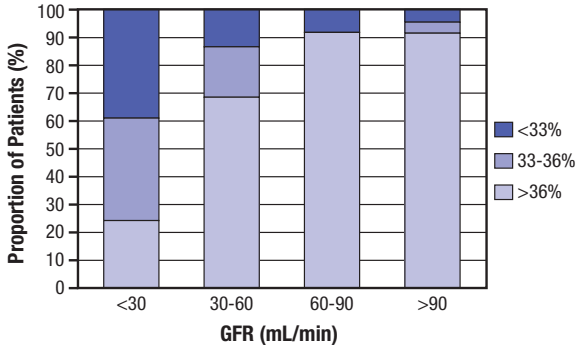
A benefit of anemia correction in patients with chronic renal failure has been demonstrated. Correction of anemia significantly improved heart and renal function in 126 patients with chronic renal failure or both chronic renal failure and CHF in a prospective study by Silverberg et al.[57] The patients were treated with subcutaneous erythropoietin and intravenous (IV) iron adjusted to achieve and maintain target hemoglobin levels of 12.5 g/dL. After treatment, patients showed statistically significant improvements in the New York Heart Association class and ejection fraction, and significantly fewer hospitalizations for CHF (*P* value at least <.05 for each parameter).

Another prospective study evaluated the impact of normalizing the hematocrit on LVH in 9 predialysis patients with chronic kidney disease and a hematocrit at baseline of <25%.[58] Patients were treated with erythropoietin and supplemental IV iron, if necessary, to achieve a target hematocrit value of 40%. Normalization of the hematocrit (40.4% in men; 37.6% in women) was associated with a significant regression of LVMI.[58]

The studies described have demonstrated an association between renal function and anemia, and a negative effect of anemia on long-term outcome following renal transplantation. Improved kidney function in the renal transplant recipient may be associated with more effective erythropoiesis.[38] Although benefits of correcting anemia in chronic renal failure have been clinically proven, the investigation, evaluation, and treatment of anemia in renal transplant recipients appears to be

Figure 5

Hematocrit Levels at Different Stages of Chronic Kidney Disease



Reprinted with permission from Mix TCH, Kazmi W, Khan S, et al. *Am J Transplant*. 2003;3:1426-1433.

suboptimal.[38] Some pharmacologic agents administered in the posttransplant period may also contribute to anemia, making it important to monitor hemoglobin levels during maintenance immunosuppressive and antihypertensive therapy. These findings underscore the need to identify and treat anemia more aggressively in patients with chronic kidney disease and in renal transplant recipients.

Hypertension

Hypertension is a well-known and well-established cardiovascular disease risk factor. It is common in renal transplant recipients and may be an important predictor of late graft loss.[9] Opelz et al reported the findings of the Collaborative Transplant Study investigating the relationship between blood pressure and long-term graft and

Table 9

Risk Factors for Death After 5 Years in 284 Renal Transplant Recipients Who Survived at Least 5 Years
(Final Cox model included left ventricular hypertrophy, age, and diabetes [model *P*<.0000001])

Variable	Relative Risk (95% CI)	*P*
LVH in fifth year	2.15 (1.14, 4.01)	.02
Age (per decade)	1.72 (1.42, 2.09)	<.001
Diabetes	3.55 (2.11, 6.00)	<.001
Hemoglobin (per 10 g/L decrease)	NS	NS
Diastolic BP (per 10 mmHg)	NS	NS
Albumin	NS	NS
Rejection in first year	NS	NS
Cadaveric donor	NS	NS
Smoking	NS	NS

NS, not significant

Reprinted with permission from Rigatto C, Foley R, Jeffery J, Negrijn C, Tribula C, Parfrey P. *J Am Soc Nephrol*. 2003;14:462-468.

patient survival in 29,751 renal transplant recipients from 262 international transplant centers.[59] Increased systolic and diastolic blood pressures 1 year after transplantation were associated with an increased risk of graft failure during the following 6 years (Figure 6).[59] In another study, a correlation between poorly controlled systemic hypertension in the early posttransplant period and poor graft survival was reported in African American kidney transplant recipients.[60]

Blood pressure control before and after transplantation is warranted, as part of best medical practice, as this measure may reduce cardiovascular disease risk as well as long-term graft loss. In addition, the choice of immunosuppressive regimen is also important, since commonly administered agents, including corticosteroids, cyclosporine, and tacrolimus have been associated with increases in the prevalence and severity of hypertension.[9]

Posttransplant diabetes mellitus

Posttransplant diabetes mellitus (PTDM), or new onset diabetes mellitus, is a prevalent posttransplant complication, particularly in the first 6 months posttransplantation, and is associated with elevated risks for cardiovascular disease, graft failure, and death.[3,43] The incidence of PTDM has increased in recent years.[61] Cosio et al analyzed data from 2078 previously nondiabetic patients who received renal transplants between 1982 and 1999 and found a 1.9 times higher incidence of PTDM in patients transplanted since 1995.

The increased incidence in PTDM appears to be multifactorial, including an increase in the age and body weight of renal transplant recipients, and a role of immunosuppressive regimens.[61] Among those regimens, corticosteroids and the calcineurin inhibitors, cyclosporine and tacrolimus, are associated with an increased risk of PTDM.[3,9,61] The risk of PTDM appears to be higher with tacrolimus than with cyclosporine. A study comparing cyclosporine and tacrolimus found that African American renal transplant recipients treated with tacrolimus had a higher risk of PTDM than Caucasian patients.[62] The TOR inhibitor sirolimus does not appear to be associated with PTDM.[9]

An analysis of USRDS data for 11,659 Medicare beneficiaries receiving first kidney transplants from 1996 through 2000 showed a cumulative incidence of PTDM of 9.1%, 16%, and 24% at 3, 12, and 36 months posttransplantation, respectively.[63] Obesity was identified as an important risk factor for PTDM, along with age, race, ethnicity, hepatitis C infection, male gender, increasing HLA mismatches, and maintenance immunosuppressive regimen.[63] The risk of PTDM in this study was 53% higher in patients treated with tacrolimus compared with patients initially treated with mycophenolate mofetil and azathioprine.[64] In this study, however, use of tacrolimus was associated with improved graft survival. Posttransplant diabetes mellitus was associated with higher rates of graft failure and mortality. Twenty-eight percent of the 923 deaths were the result of cardiovascular disease.

A retrospective chart review of 939 patients who received renal transplants between 1984 and 1999 showed that 5.1% developed PTDM.[65] Patient survival was adversely affected by both pre-existing diabetes and by PTDM.[66] Patients with a family history of diabetes, abnormal glucose tolerance, obesity, and certain subpopulations, including African Americans, males, and older persons (aged >45 years), are at increased risk for PTDM.[3,61,63,66] The risk for PTDM should be assessed prior to transplantation and this information will help with the selection of the initial immunosuppressive regimen. Immunosuppressive regimens for patients at high risk for PTDM should be identified, and appropriate treatment measures should be instituted early in the posttransplant period to minimize the consequences of PTDM.

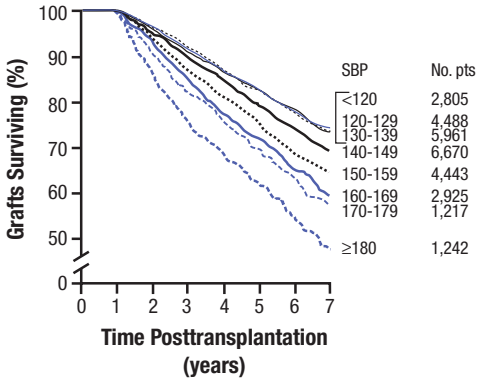
Hyperlipidemia

Hyperlipidemia is also a known risk factor for the development of cardiovascular disease in any population. Elevations of total serum cholesterol, low density lipoprotein (LDL) cholesterol, and triglycerides occur frequently among renal transplant recipients.[48] Interestingly, levels of high-density lipoprotein cholesterol are typically normal.[48]

Multiple causes of hyperlipidemia in renal transplant recipients have been proposed, including graft dysfunction and a high prevalence of diabetes, older age, hypertension, and increased body mass index.[9] Immunosuppressive agents may also contribute to dyslipidemias following renal transplantation. Corticosteroids, cyclosporine, tacrolimus, and sirolimus have all been associated with dyslipidemias to different degrees. The effect of sirolimus appears to be greater than that of cyclosporine and tacrolimus; however,[9] in most cases, lipid level elevations associated with sirolimus are treatable and/or reversible.[9]

Figure 6

Association of Hypertension at 1 Year With Decreased Graft Survival



SBP, systolic blood pressure.

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Epidemiologic studies have identified lipoprotein(a) as a possible independent risk factor for atherosclerosis.[67] A study reported by Sechi et al measured serum lipoprotein(a) levels in 257 patients with normal renal function (creatinine clearance ≥90 mL/min/1.73 m^2) and in 160 patients with mild to moderate renal dysfunction (creatinine clearance 30-89 mL/min/1.73 m^2).[67] Age and prevalence of hypertension were significantly higher in the group of patients with kidney failure (Table 10). The patients with mild to moderate renal dysfunction had significantly higher serum lipoprotein(a) levels than those with normal renal function (*P*<.001) [Table 11]. Serum lipoprotein(a) was directly associated with the severity of renal function impairment. A discriminant analysis revealed that age, blood pressure, and serum lipoprotein(a) were independently associated with early renal failure.

A randomized study compared tacrolimus to cyclosporine in 53 renal transplant recipients with hyperlipidemia and stable graft function (transplant age, 38-42 mo).[68] Conversion from maintenance cyclosporine based immunosuppressive specimen to tacrolimus was associated with significant decreases in total cholesterol (*P*=.0031), LDL cholesterol (*P*=.0014), and apolipoprotein B (*P*=.034) by the first month after conversion.[68] No changes in renal function or glycemic control were observed, however, in patients treated with tacrolimus.[68]

Homocysteine and advanced glycation end-products

Homocysteine and advanced glycosylation end-products (AGEs), now recognized as nontraditional cardiovascular disease risk factors, may play a role in cardiovascular disease development in the renal transplant population.[49,69] An independent association between serum homocysteine levels and cardiovascular events was demonstrated in 207 stable renal transplant recipients (transplant duration >6 months) who were followed for 14 to 26 months.[50] One or more cardiovascular events (cerebrovascular disease, coronary disease, or peripheral vascular disease) occurred in 14.5% of patients, and four patients (1.9%) died of cardiovascular causes during follow-up.[50] Serum homocysteine levels were significantly higher in patients experiencing cardiovascular events versus those without a cardiovascular event (33 mmol/L vs 19 mmol/L, respectively; *P*<.001). The relative risk for future cardiovascular events increased 6% per mmol/L increase in serum homocysteine levels.

Plasma concentrations of pentosidine, a pentose-derived AGE, were measured in 3 groups of patients with ESRD: patients with diabetes undergoing kidney-pancreas transplantation (n=38), patients with diabetes undergoing kidney transplantation (n=44), and patients without diabetes undergoing kidney transplantation (n=46).[49] Prior to transplantation, plasma pentosidine was 20 to 35 times higher in the 3 study groups than in normal volunteers. Following transplantation, plasma pentosidine levels were reduced significantly in all groups within 3 months of transplantation but remained significantly above the normal level in normal subjects more than 2 years following transplantation. A correlation between plasma pentosidine levels and serum creatinine concentrations suggested that persistent elevations of AGEs were related to impaired renal function after transplantation.

Additional research is needed to increase our understanding of the role of AGEs, homocysteine, and other nontraditional risk factors in the development of cardiovascular disease in patients with chronic kidney disease. The findings will help to determine if interventions directed to modify the impact of these nontraditional cardiovascular disease risk factors may be warranted.

Table 10

Decreased Glomerular Filtration Rate and Plasma Lipids

	Creatinine Clearance (mL/min/1.73 m^2)	
Patient Characteristic	**≥90 (n=257)**	**30-89 (n=160)**
Age (y)	51±13	59±13*
Ccl (mL/min/1.73 m^2)	118±24	67±18*
Hypertension (%)	72.4	86.9*
Urine albumin (mg/d)	21±28	55±153
Uric acid (mmol/L)	363±48	464±42*

**P*<.001

Adapted with permission from Sechi LA, Zingaro L, De Carli S, et al. *Ann Intern Med*. 1998;129:457-461.

Table 11

Decreased Glomerular Filtration Rate and Plasma Lipids

	Creatinine Clearance (mL/min/1.73 m^2)	
Lipid Parameter	**≥90 (n=257)**	**30-89 (n=160)**
Cholesterol (mmol/L)	5.28±1.11	5.44±1.12
HDL (mmol/L)	1.31±0.39	1.38±0.38
LDL (mmol/L)	3.33±1.02	3.44±0.89
Triglycerides (mmol/L)	1.44±0.90	1.55±0.88
Lipoprotein(a) (mg/dL)	14.4±16.7	23.0±24.5*

**P*<.001.

Adapted with permission from Sechi LA, Zingaro L, De Carli S, et al. *Ann Intern Med*. 1998;129:457-461.

Conclusions

Graft and patient survival following renal transplantation continue to improve.[8] Since 1995, 1-year graft survival has improved steadily.[3] Progress has been attributed to improvements in immunosuppressive regimens, surgical techniques, and posttransplant care.[70] The rate of late graft failure, however, as measured by the half-lives of grafts that survive at least 1 year, has changed very little since 1995.[3] Known predictors of late graft loss include recipient age, donor age, recipient race, pretransplant dialysis requirements, diabetes, delayed graft function, and HLA-mismatch.[12] Renal function in the first year after transplantation is an important predictor of long-term graft survival.[12] Renal function at 1 year following transplantation also appears to be independently associated with the incidence and risk of cardiovascular death.[13]

Renal function in the first year following transplantation has improved in recent years.[12] This improvement may be due to better diagnosis and management of acute rejection and subacute clinical rejection, and reduced incidences of death with a functioning graft and HLA mismatching. Better control of hypertension and dyslipidemia and increased awareness and reduction of calcineurin-inhibitor related nephrotoxicity may also be factors.[12]

Renal dysfunction is associated with traditional cardiovascular disease risk factors, such as hypertension and dyslipidemias, as well as substances more recently linked to cardiovascular disease, such as homocysteine. Although additional research is needed to clarify these findings and their implications, the observations made to date suggest the need to emphasize measurement and preservation of renal function to the same degree that prevention of rejection in post-renal transplantation care is emphasized. These findings also raise the possibility of using the serum creatinine level as a surrogate endpoint for clinical trials evaluating and comparing posttransplant immunosuppression and management protocols.[12]

The high prevalence of cardiovascular disease in renal transplant recipients is likely attributable to both pretransplant and posttransplant risk factors. Clinicians need to identify pretransplant cardiovascular risk factors and actively apply interventions to modify those risk factors accordingly. Prior to transplantation, correction of hypertension, intensive treatment of diabetes mellitus, smoking cessation, weight reduction, and correction of anemia, may help to reduce cardiovascular risk post-transplantation.[43] Following transplantation, detection and appropriate treatment of hypertension, recognition and correction of anemia, identification and management of hyperlipidemia and diabetes, avoidance of smoking, and the addition of regular physical activity may also reduce cardiovascular disease. The benefits of measures directed to modify nontraditional cardiovascular disease risk factors has not yet been demonstrated.

Adverse effects of immunosuppressive agents may raise cardiovascular disease risk as well; careful selection of immunosuppressive regimens and monitoring during therapy may help to optimize the cardiovascular disease risk profile. Initial immunosuppressive regimens should be selected with consideration of pre-existing cardiovascular disease risk. If monitoring during treatment reveals hyperlipidemia, PTDM, hypertension, or other cardiovascular disease risk-factor elevation that may be drug induced, dosage reduction, drug withdrawal, or therapy substitution should be considered. Investigations of the contribution of various agents and combinations to cardiovascular disease risk and outcome are continuing. These findings will help to guide clinicians in the selection of individualized regimens that provide the optimal balance of efficacy and safety both in the short-term and long-term phases of posttransplant care.

The impact of newer immunosuppressive agents on long-term outcomes following withdrawal of cyclosporine and tacrolimus is yet to be seen in a large patient population.[70] Early experience with newer agents, such as mycophenolate mofetil and sirolimus, is promising. These agents may offer immunosuppressive efficacy with lower toxicity, potentially improving long-term outcomes. In the past, immunosuppression was primarily directed to reduce acute rejection in the first 6 months to 1 year after transplantation. Today, renal transplant recipients are appreciating increased life expectancy. Immunosuppression and other posttransplant care strategies must focus on the issues that threaten graft and patient survival beyond the first year. Toxicities associated with ongoing administration of steroids and calcineurin inhibitors can be minimized. Following a cardiovascular disease risk assessment, regimens can be chosen that minimize the potential for common complications, such as hypertension, anemia, PTDM, and hyperlipidemia. When adverse effects of therapy are identified, aggressive, appropriate treatment measures can be implemented.

In the future, we can also expect an improved ability to diagnose signs of rejection in the posttransplant period. Investigations of the associations between morphologic findings and acute and chronic rejection and clinical outcome are continuing. New knowledge will lead to continued refinements of the Banff Classification schema and improved differential diagnostic capabilities. We can expect the emphasis in biopsy assessment to eventually shift from diagnosis to prediction of late graft function and outcome, which will facilitate earlier intervention.[44] In addition, new noninvasive molecular biology alternatives to biopsy are anticipated, tools that may further improve our ability to accurately diagnose rejection and other conditions early in the posttransplant period and to intervene accordingly.

The combination of improved diagnostic capabilities and refined immunosuppression and patient care strategies may decrease cardiovascular disease morbidity and mortality and improve long-term outcomes in renal transplant recipients. Knowledge gained in the process may also help to identify opportunities for intervention that may reduce the burden of cardiovascular disease in patients with earlier stages of renal disease.

Understanding the Relationship Between Renal Dysfunction and Cardiovascular Disease After Renal Transplantation

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Post-test Answer Key

1.	A	B	C	D	3.	A	B			5.	A	B	C	D	7.	A	B	C	D	9.	A	B	C	D	11.	A	B	C	D	13.	A	B	C	D
2.	A	B	C	D	4.	A	B	C	D	6.	A	B	C	D	8.	A	B	C	D	10.	A	B	C	D	12.	A	B	C	D	14.	A	B	C	D

POST-TEST

1. According to the National Kidney Foundation K/DOQI Practice Guidelines for chronic kidney disease, what glomerular filtration rate (GFR) corresponds to loss of >50% of the adult level of normal kidney function?
   a. <90 mL/min/1.73 m^2
   b. <60 mL/min/1.73 m^2
   c. <50 mL/min/1.73 m^2
   d. <30 mL/min/1.73 m^2

2. The more frequent cause of death in renal transplant recipients is:
   a. Cardiovascular disease
   b. Infection
   c. Cancer
   d. Graft failure

3. Traditional cardiovascular risk factors, including hypertension, hyperlipidemia, diabetes, and older age, are more prevalent in patients with chronic kidney disease than in the general population. (True or False)
   a. True
   b. False

4. C-reactive protein is a marker for:
   a. Inflammation
   b. Infection
   c. Nephrotoxicity
   d. Immunodeficiency

5. In the United States, the expected remaining lifetimes for dialysis patients are _____ that of the general population.
   a. 1/8-1/4
   b. 1/3-1/6
   c. 1/2
   d. 2/3

6. The annual cardiovascular disease mortality rate for renal transplant recipients is _____.
   a. 1.0%
   b. 0.5%
   c. 0.3%
   d. 0.2%

7. Renal function in the first year following renal transplantation was shown to be a strong predictor of:
   a. Long-term graft survival
   b. Long-term patient survival
   c. Short-term graft survival
   d. Short-term patient survival

8. An analysis of USRDS data for 58,900 adult renal transplant recipients revealed a correlation between the time a patient spent on dialysis and:
   a. Cardiovascular death
   b. Hypertension
   c. Anemia
   d. Acute rejection

9. Which of the following are calcineurin inhibitors?
   a. Sirolimus
   b. Tacrolimus
   c. Mycophenolate mofetil
   d. Azathioprine

10. In the Banff `97 Classification schema, a diagnosis of graft rejection is based mainly on 2 lesions: _____ and _____.
    a. Interstitial inflammation and glomerulitis
    b. Glomerulitis and tubulitis
    c. Tubulitis and interstitial inflammation
    d. Arteritis and tubulitis

11. Anemia is a late complication of kidney transplantation in _____ of patients.
    a. 5%
    b. 10%
    c. 30%
    d. 50%

12. Studies reveal associations between anemia in renal transplant patients and the administration of:
    a. Beta-blockers
    b. Calcium channel inhibitors
    c. Angiotensin-converting enzyme inhibitors
    d. Diuretics

13. Left ventricular hypertrophy in the first year following renal transplantation was predictive of _____ and death.
    a. Coronary artery disease
    b. Myocardial infarction
    c. Rejection
    d. Congestive heart failure

14. Which of the following medications is associated with an increased risk of posttransplant diabetes mellitus (PTDM)?
    a. Cyclosporine
    b. Tacrolimus
    c. Corticosteroids
    d. All of the above

Understanding the Relationship Between Renal Dysfunction and Cardiovascular Disease After Renal Transplantation

Program Evaluation

The University of Minnesota would appreciate your comments regarding the quality of the information presented.

1. The program objectives were fully met.

   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree

2. The quality of the educational process (method of presentation and information provided) was satisfactory and appropriate.

   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree

3. This educational activity has enhanced my professional effectiveness and improved my ability to treat/manage patients.

   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree ❑ N/A

4. This educational activity has enhanced my professional effectiveness and improved my ability to communicate with patients.

   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree ❑ N/A

5. The information presented was *without* promotional or commercial bias.

   ❑ Agree ❑ Disagree

6. What changes will you make in your practice as a result of participating in this program?

   _____

   _____

7. Comments/suggestions regarding *this* material.

   _____

   _____

8. Recommendations for *future* presentations.

   _____

   _____

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References

1. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med.* 2003;139(2):137-147.
2. NKF. K/DOQI Clinical Practice Guidelines for CKD. *Am J of Kidney Diseases.* 2002;39(2):S17-S31.
3. United States Renal Data System. 2003 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2003. Available at: http://www.usrds.org/2003/pdf/01_ckd_03.pdf. Accessed December 6, 2003.
4. Shlipak MG, Simon JA, Grady D, Lin F, Wenger NK, Furberg CD. Renal insufficiency and cardiovascular events in postmenopausal women with coronary heart disease. *J Am Coll Cardiol.* 2001;38(3):705-711.
5. Fried LF, Shlipak MG, Crump C, et al. Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. *J Am Coll Cardiol.* 2003;41(8):1364-1372.
6. Levey AS, Beto JA, Coronado BE, et al. Controlling the epidemic of cardiovascular disease in chronic renal disease: executive summary. Report from the National Kidney Foundation Task Force on Cardiovascular Disease, October 1998. Available at: http://www.kidney.org/professionals/physfile/cardiointro.cfm. Accessed January 28, 2004.
7. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis.* 1998;32(5 Suppl 3):S112-119.
8. Aker S, Ivens K, Grabensee B, Heering P. Cardiovascular risk factors and diseases after renal transplantation. *Int Urol Nephrol.* 1998;30(6):777-788.
9. Kasiske BL, Ballantyne CM. Cardiovascular risk factors associated with immunosuppression in renal transplantation. *Transpl Rev.* 2002;16:1-21.
10. Muntner P, Hamm LL, Kusek JW, Chen J, Whelton PK, He J. The prevalence of nontraditional risk factors for coronary heart disease in patients with chronic kidney disease. *Ann Intern Med.* Jan 6 2004;140(1):9-17.
11. Sarnak MJ, Levey AS. Cardiovascular disease and chronic renal disease: a new paradigm. *Am J Kidney Dis.* 2000;35 (4 suppl 1):S117-131.
12. Hariharan S, McBride MA, Cherikh WS, Tolleris CB, Bresnahan BA, Johnson CP. Post-transplant renal function in the first year predicts long-term kidney transplant survival. *Kidney Int.* 2002;62(1):311-318.
13. Meier-Kriesche HU, Baliga R, Kaplan B. Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. *Transplantation.* 2003;75(8):1291-1295.
14. Feldman HI, Appel LJ, Chertow GM, et al. The Chronic Renal Insufficiency Cohort (CRIC) Study: Design and Methods. *J Am Soc Nephrol.* 2003;14(7 suppl 2):S148-153.
15. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis.* Jan 2003;41(1):1-12.
16. Twenty million Americans with chronic kidney disease in highest risk group for cardiovascular disease: new National Kidney Foundation-K/DOQI guidelines urge physicians to test and treat chronic kidney disease patients for dyslipidemias [press release]. New York: National Kidney Foundation; April 2, 2003. Available at: http://www.kidney.org/general/news/newsitem.cfm?id=182. Accessed January 28, 2004.
17. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Ann Intern Med.* 2001;134(8):629-636.
18. Shulman NB, Ford CE, Hall WD, et al. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Program Cooperative Group. *Hypertension.* 1989;13(5 suppl):I80-93.
19. Ruilope LM, Salvetti A, Jamerson K, et al. Renal function and intensive lowering of blood pressure in hypertensive participants of the hypertension optimal treatment (HOT) study. *J Am Soc Nephrol.* 2001;12(2):218-225.
20. Culleton BF, Larson MG, Evans JC, et al. Prevalence and correlates of elevated serum creatinine levels: the Framingham Heart Study. *Arch Intern Med.* 1999;159(15):1785-1790.
21. Culleton BF, Larson MG, Wilson PW, Evans JC, Parfrey PS, Levy D. Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int.* 1999;56(6):2214-2219.
22. Shlipak MG, Heidenreich PA, Noguchi H, Chertow GM, Browner WS, McClellan MB. Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med.* 2002;137(7):555-562.
23. Best PJ, Lennon R, Ting HH, et al. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol.* 2002;39(7):1113-1119.
24. Stuveling EM, Hillege HL, Bakker SJ, Gans RO, De Jong PE, De Zeeuw D. C-reactive protein is associated with renal function abnormalities in a non-diabetic population. *Kidney Int.* 2003;63(2):654-661.
25. Stam F, van Guldener C, Schalkwijk CG, ter Wee PM, Donker AJ, Stehouwer CD. Impaired renal function is associated with markers of endothelial dysfunction and increased inflammatory activity. *Nephrol Dial Transplant.* 2003;18(5):892-898.
26. Panichi V, Migliori M, De Pietro S, et al. C-reactive protein in patients with chronic renal diseases. *Ren Fail.* 2001;23(3-4): 551-562.
27. Kubo M, Kiyohara Y, Kato I, et al. Effect of hyperinsulinemia on renal function in a general Japanese population: the Hisayama study. *Kidney Int.* 1999;55(6):2450-2456.
28. Fliser D, Pacini G, Engelleiter R, et al. Insulin resistance and hyperinsulinemia are already present in patients with incipient renal disease. *Kidney Int.* 1998;53(5):1343-1347.
29. Wannamethee SG. Serum uric acid is not an independent risk factor for coronary heart disease. *Curr Hypertens Rep.* 2001;3(3):190-196.
30. Alderman MH. Serum uric acid as a cardiovascular risk factor for heart disease. *Curr Hypertens Rep.* 2001;3(3):184-189.
31. Hedback GM, Oden AS. Cardiovascular disease, hypertension and renal function in primary hyperparathyroidism. *J Intern Med.* 2002;251(6):476-483.
32. Pitts TO, Piraino BH, Mitro R, et al. Hyperparathyroidism and 1,25-dihydroxyvitamin D deficiency in mild, moderate, and severe renal failure. *J Clin Endocrinol Metab.* 1988;67(5): 876-881.
33. Reichel H, Deibert B, Schmidt-Gayk H, Ritz E. Calcium metabolism in early chronic renal failure: implications for the pathogenesis of hyperparathyroidism. *Nephrol Dial Transplant.* 1991;6(3):162-169.
34. Hall JE, Hildebrandt DA, Kuo J. Obesity hypertension: role of leptin and sympathetic nervous system. *Am J Hypertens.* 2001;14(6 Pt 2):103S-115S.
35. Wallace AM, McMahon AD, Packard CJ, et al. Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS). *Circulation.* 2001;104(25):3052-3056.
36. Chu NF, Spiegelman D, Hotamisligil GS, Rifai N, Stampfer M, Rimm EB. Plasma insulin, leptin, and soluble TNF receptors levels in relation to obesity-related atherogenic and thrombogenic cardiovascular disease risk factors among men. *Atherosclerosis.* 2001;157(2):495-503.
37. Vanrenterghem Y. Prevalence and management of anaemia in transplant patients. *Nephrol Dial Transplant.* 2002;17 (suppl 1):47.
38. Mix TC, Kazmi W, Khan S, et al. Anemia: a continuing problem following kidney transplantation. *Am J Transplant.* 2003;3(11):1426-1433.
39. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med.* 1999;341(23):1725-1730.
40. Ojo AO, Hanson JA, Wolfe RA, Leichtman AB, Agodoa LY, Port FK. Long-term survival in renal transplant recipients with graft function. *Kidney Int.* 2000;57(1):307-313.
41. Beers MH, Berkow R, eds. The Merck Manual of Diagnosis and Therapy, Section 12, Immunology: Allergic disorders. Chapter 149, Transplantation. Available at: http://www.merck.com/mrkshared/mmanusal/section12/chapter149/149b.jsp. Accessed January 26, 2004.
42. Formica RN Jr, Lorber KM, Friedman AL, et al. Sirolimus-based immunosuppression with reduced dose cyclosporine or tacrolimus after renal transplantation. *Transplant Proc.* 2003;35(3 suppl):95S-98S.
43. Ponticelli C, Villa M. Role of anaemia in cardiovascular mortality and morbidity in transplant patients. *Nephrol Dial Transplant.* 2002;17(suppl 1):41-46.
44. Racusen LC, Solez K, Colvin RB, et al. The Banff 97 working classification of renal allograft pathology. *Kidney Int.* 1999;55(2):713-723.
45. Solez K, Racusen LC. Acute renal failure in the transplanted kidney. In: Schrier RW, ed. Atlas of Diseases of the Kidney. Available at: http://cnserver0.nkf.med.ualberta.ca/cn/Schrier/Volume1/chap10/ADK1_10_1-3.pdf. Accessed January 28, 2004.
46. Djamali A, Becker YT, Simmons WD, Johnson CA, Premasathian N, Becker BN. Increasing hematocrit reduces early posttransplant cardiovascular risk in diabetic transplant recipients. *Transplantation.* 2003;76(5):816-820.
47. Rigatto C, Foley R, Jeffery J, Negrijn C, Tribula C, Parfrey P. Electrocardiographic left ventricular hypertrophy in renal transplant recipients: prognostic value and impact of blood pressure and anemia. *J Am Soc Nephrol.* 2003;14(2): 462-468.
48. Kasiske BL. Hyperlipidemia in patients with chronic renal disease. *Am J Kidney Dis.* 1998;32(5 suppl 3):S142-156.
49. Hricik DE, Schulak JA, Sell DR, Fogarty JF, Monnier VM. Effects of kidney or kidney-pancreas transplantation on plasma pentosidine. *Kidney Int.* 1993;43(2):398-403.
50. Ducloux D, Motte G, Challier B, Gibey R, Chalopin JM. Serum total homocysteine and cardiovascular disease occurrence in chronic, stable renal transplant recipients: a prospective study. *J Am Soc Nephrol.* 2000;11(1):134-137.
51. Ducloux D, Challier B, Saas P, Tiberghien P, Chalopin JM. CD4 cell lymphopenia and atherosclerosis in renal transplant recipients. *J Am Soc Nephrol.* 2003;14(3):767-772.
52. Brennan DC. Conference Report. XIX International Congress of the Transplantation Society. Medscape Transplantation [serial online]. Vol 3; 2002:1-7.
53. Vanrenterghem Y, Ponticelli C, Morales JM, et al. Prevalence and management of anemia in renal transplant recipients: a European survey. *Am J Transplant.* 2003;3(7):835-845.
54. Kiberd B, Keough-Ryan T, Panek R. Cardiovascular disease reduction in the outpatient kidney transplant clinic. *Am J Transplant.* 2003;3(11):1393-1399.
55. Yorgin PD, Scandling JD, Belson A, Sanchez J, Alexander SR, Andreoni KA. Late posttransplant anemia in adult renal transplant recipients. An under-recognized problem? *Am J Transplant.* 2002;2(5):429-435.
56. Levin A, Thompson CR, Ethier J, et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis.* 1999;34(1):125-134.
57. Silverberg DS, Wexler D, Blum M, et al. Aggressive therapy of congestive heart failure and associated chronic renal failure with medications and correction of anemia stops or slows the progression of both diseases. *Perit Dial Int.* 2001;21(suppl 3): S236-240.
58. Hayashi T, Suzuki A, Shoji T, et al. Cardiovascular effect of normalizing the hematocrit level during erythropoietin therapy in predialysis patients with chronic renal failure. *Am J Kidney Dis.* 2000;35(2):250-256.
59. Opelz G, Wujciak T, Ritz E. Association of chronic kidney graft failure with recipient blood pressure. Collaborative Transplant Study. *Kidney Int.* 1998;53(1):217-222.
60. Cosio FG, Dillon JJ, Falkenhain ME, et al. Racial differences in renal allograft survival: the role of systemic hypertension. *Kidney Int.* 1995;47(4):1136-1141.
61. Cosio FG, Pesavento TE, Osei K, Henry ML, Ferguson RM. Post-transplant diabetes mellitus: increasing incidence in renal allograft recipients transplanted in recent years. *Kidney Int.* Feb 2001;59(2):732-737.
62. Neylan JF. Racial differences in renal transplantation after immunosuppression with tacrolimus versus cyclosporine. FK506 Kidney Transplant Study Group. *Transplantation.* 1998;65(4):515-523.
63. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant.* 2003;3(2):178-185.
64. Pirsch JD, Miller J, Deierhoi MH, Vincenti F, Filo RS. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. FK506 Kidney Transplant Study Group. *Transplantation.* 1997;63(7):977-983.
65. Revanur VK, Jardine AG, Kingsmore DB, Jaques BC, Hamilton DH, Jindal RM. Influence of diabetes mellitus on patient and graft survival in recipients of kidney transplantation. *Clin Transplant.* 2001;15(2):89-94.
66. Weir MR, Fink JC. Risk for posttransplant Diabetes mellitus with current immunosuppressive medications. *Am J Kidney Dis.* 1999;34(1):1-13.
67. Sechi LA, Zingaro L, De Carli S, et al. Increased serum lipoprotein(a) levels in patients with early renal failure. *Ann Intern Med.* 1998;129(6):457-461.
68. McCune TR, Thacker LR, II, Peters TG, et al. Effects of tacrolimus on hyperlipidemia after successful renal transplantation: a Southeastern Organ Procurement Foundation multicenter clinical study. *Transplantation.* 1998;65(1):87-92.
69. Eikelboom JW, Lonn E, Genest J Jr, Hankey G, Yusuf S. Homocyst(e)ine and cardiovascular disease: a critical review of the epidemiologic evidence. *Ann Intern Med.* 1999;131(5):363-375.
70. Lo A, Alloway RR. Strategies to reduce toxicities and improve outcomes in renal transplant recipients. *Pharmacotherapy.* Mar 2002;22(3):316-328.

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All correspondence concerning the contents of this publication should be directed to:

SynerMed® Communications
Dept. WA46D-131
405 Trimmer Road
PO Box 458
Califon, NJ 07830

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